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TERMINAL (ENTER 1, 2, 3, 4, OR ?):3
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L1   (    52891)TISSUE
L2   (   183294)FACTOR
L3   (    37952)PROTEIN
L4          11 TISSUE(W)FACTOR(W)PROTEIN

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US PAT NO:      5,298,599 [IMAGE AVAILABLE]            L4: 1 of 11
TITLE:          Expression and purification of recombinant soluble tissue
                  factor

US PAT NO:      5,262,322 [IMAGE AVAILABLE]            L4: 2 of 11
TITLE:          Host transformed with yeast gene and ubiquitin/polypeptide
                  fusions

US PAT NO:      5,223,427 [IMAGE AVAILABLE]            L4: 3 of 11
TITLE:          Hybridomas producing monoclonal antibodies reactive with
                  human tissue-factor glycoprotein heavy chain

US PAT NO:      5,223,408 [IMAGE AVAILABLE]            L4: 4 of 11
TITLE:          Method for making variant secreted proteins with altered
                  properties

US PAT NO:      5,219,752 [IMAGE AVAILABLE]            L4: 5 of 11
TITLE:          Process for continuously culturing adherent animal cells

US PAT NO:      5,192,743 [IMAGE AVAILABLE]            L4: 6 of 11
TITLE:          Reconstitutable lyophilized protein formulation

US PAT NO:      5,110,730 [IMAGE AVAILABLE]            L4: 7 of 11
TITLE:          Human tissue factor related DNA segments

US PAT NO:      5,108,919 [IMAGE AVAILABLE]            L4: 8 of 11
TITLE:          DNA sequences encoding yeast ubiquitin hydrolase

US PAT NO:      5,024,939 [IMAGE AVAILABLE]            L4: 9 of 11
TITLE:          Transient expression system for producing recombinant
                  protein

US PAT NO:      5,017,556 [IMAGE AVAILABLE]            L4: 10 of 11
TITLE:          Treatment of bleeding disorders using lipid-free
                   tissue    factor    protein

US PAT NO:      4,865,984 [IMAGE AVAILABLE]            L4: 11 of 11
TITLE:          Dynamic continuous flow enzyme reactor

9}1@ cidt ,cfidt,,rfedl,,rkewli,ck w1i,c4 ,17,,49,,71,0

1.  5,298,599, Mar. 29, 1994, Expression and purification of recombinant
soluble tissue factor; Alireza Rezaie, et al., 530/350; 435/68.1, 69.6,
69.7; 530/381, 388.25, 413 [IMAGE AVAILABLE]

US PAT NO:      5,298,599 [IMAGE AVAILABLE]            L4: 1 of 11
DATE FILED:     Jan. 3, 1992
REL-US-DATA:    Continuation-in-part of Ser. No. 730,040, Jul. 12, 1991,
                  Pat. No. 5,202,253, which is a continuation of Ser. No.
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Ser. No. 683,682, Apr. 10, 1991.

DETDESC:

DETD(30)

The . . . sequence described in U.S. Ser. No. 07/683,682 filed Apr 10, 1991, the teachings of which are incorporated herein. The truncated tissue factor protein lacks the predicted transmembrane and cytoplasmic domains of tissue factor. The essential difference between truncated tissue factor and wild-type tissue. . .

DETDESC:

DETD(45)

Approximately . . . SDS gel electrophoresis. The tissue factor runs as monomer in the gel even without disulfide bond reduction. The soluble, truncated tissue factor protein isolated in this manner has full cofactor activity toward factor VIIa even without the HPC-4 epitope removed; this activity is. . .

4. 5,223,408, Jun. 29, 1993, Method for making variant secreted proteins with altered properties; David V. Goeddel, et al., 435/69.3, 69.4, 69.52, 69.6, 69.7, 172.3, 189, 195, 215, 216, 226 [IMAGE AVAILABLE]

US PAT NO: 5,223,408 [IMAGE AVAILABLE] L4: 4 of 11
DATE FILED: Jul. 11, 1991

SUMMARY:

BSUM(33)

The . . . IX, thrombin, hemopoietic growth factor, tumor necrosis factor-alpha and -beta, enkephalinase, human serum albumin, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, .beta.-lactamase, tissue factor protein , inhibin, activin, vascular endothelial growth factor, integrin receptors, thrombopoietin, protein A or D, rheumatoid factors, NGF-.beta., platelet-growth factor, transforming growth. . .

DETDESC:

DETD(73)

This . . . as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a microbial protein, such as .beta.-lactamase; tissue factor protein ; inhibin; activin; vascular endothelial growth factor; receptors for hormones or growth factors; integrin; thrombopoietin; protein A or D; rheumatoid factors;. . .

CLAIMS:

CLMS(9)

9. . . . IX, thrombin, hemopoietic growth factor, tumor necrosis factor-alpha and -beta, enkephalinase, human serum albumin, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, .beta.-lactamase, tissue factor protein , inhibin, activin, vascular endothelial growth factor, integrin receptors, thrombopoietin, protein A or D, rheumatoid factors, NGF-.beta., platelet-growth factor, transforming growth. . .

7. 5,110,730, May 5, 1992, Human tissue factor related DNA segments;

27 [IMAGE AVAILABLE]

US PAT NO: 5,110,730 [IMAGE AVAILABLE] L4: 7 of 11
DATE FILED: Jun. 25, 1987
REL-US-DATA: Continuation-in-part of Ser. No. 33,047, Mar. 31, 1987, abandoned.

SUMMARY:

BSUM(9)

More . . . U.S.A., 83:299-302 (1986) have reported isolating human tissue factor (huTF) protein using a method based on the discovery that delipidated tissue factor protein can bind factor VII/VIIa when the protein is solubilized in an aqueous solution containing a non-ionic detergent and CaCl.sub.2. However, the utility of that method, which employs a factor VII/VIIa affinity sorbent, as a means for isolating tissue factor protein is limited not only by the difficulty in obtaining significant quantities of isolated factor VII/VIIa but also by the lability. . .

9. 5,024,939, Jun. 18, 1991, Transient expression system for producing recombinant protein; Cornelia M. Gorman, 435/69.1, 172.3 [IMAGE AVAILABLE]

US PAT NO: 5,024,939 [IMAGE AVAILABLE] L4: 9 of 11
DATE FILED: Sep. 25, 1987
REL-US-DATA: Continuation-in-part of Ser. No. 71,674, Jul. 9, 1987, abandoned, which is a continuation-in-part of Ser. No. 907,185, Sep. 12, 1986, abandoned.

DETDESC:

DETD(4)

"Desired . . . factor VIII, tissue plasminogen activator, tumor necrosis factor alpha and beta, lymphotoxin, enkephalinase, human serum albumin, mullerian inhibiting substance, relaxin, tissue factor protein , inhibin, erythropoietin, interferon alpha, beta and gamma, superoxide dismutase, decay accelerating factor, viral antigen such as, for example, a portion. . .

10. 5,017,556, May 21, 1991, Treatment of bleeding disorders using lipid-free tissue factor protein ; Donogh P. O'Brien, et al., 514/2, 8, 21; 530/359, 380, 381, 382, 383, 384, 395, 422, 424, 829, 830 [IMAGE AVAILABLE]

US PAT NO: 5,017,556 [IMAGE AVAILABLE] L4: 10 of 11
DATE FILED: Mar. 8, 1989
REL-US-DATA: Continuation of Ser. No. 110,255, Oct. 20, 1987, abandoned, which is a continuation-in-part of Ser. No. 926,977, Nov. 4, 1986, abandoned.
TITLE: Treatment of bleeding disorders using lipid-free tissue factor protein

ABSTRACT:
A . . . of bleeding disorders, for example those characterized by a tendency toward hemorrhage or a hypercoagulative state, by the administration of tissue factor protein or antagonists thereof.

SUMMARY:

BSUM(2)

This in vitro ... Abs to the treatment of bleeding disorde ... I

particular, this invention relates to the use of tissue factor protein to effect haemostasis in certain clinical conditions and particularly in animals lacking certain coagulation proteins. Factor VIII and factor IX. . .

SUMMARY:

BSUM(6)

Tissue . . . to have a relative molecular mass of 42,000 to 53.000. Human tissue thromboplastin has been described as consisting of a tissue factor protein inserted into phospholipid bilayer in an optimal ratio of tissue factor protein :phospholipid of approximately 1:80 Lyberg, T. and Prydz. H., Nouv. Rev Fr. Hematol 25(5), 291-293 (1983). Purification of tissue factor has. . . et al., J. Biol. Chem. 260(20), 10917-10920 (1985) It is widely accepted that while there are differences in structure of tissue factor protein between species there are no functional differences as measured by in vitro coagulation assays. Guha et al. supra. Furthermore, tissue. . .

SUMMARY:

BSUM(14)

Yet another object of this invention is to provide an anticoagulant therapeutic, that is an antagonist to tissue factor protein , to neutralize the thrombotic effects of endogenous release of tissue thromboplastin which may result in a hypercoagulative state. Particularly, such an anticoagulant, that is an antagonist to tissue factor protein , would neutralize the hypercoagulant effects of endogenously released tissue thromboplastin by inactivating tissue factor protein . Such a tissue factor protein antagonist can be an antibody or other protein that specifically inactivates the protein component.

SUMMARY:

BSUM(16)

This invention is based in part on the novel and unexpected observation that infusion of tissue factor protein into rabbits lacking coagulation factors not only corrected haemostatic deficiency but did not induce disseminated intravascular coagulation or result in other adverse side effects. Tissue factor protein is the protein portion of tissue factor lacking the naturally occurring phospholipid, which was previously referred to as tissue factor apoprotein III and previously believed to be inactive. Tissue factor protein was for the first time found to correct the bleeding diathesis, i.e. a tendency toward hemorrhage, associated with factor VIII deficiency in vivo. Furthermore, infusion of tissue factor protein would be expected to be ineffective in light of the papers which describe tissue factor as having an absolute requirement. . .

SUMMARY:

BSUM(17)

Accordingly, in one aspect the invention is directed to administration of a pharmaceutical composition comprising tissue factor protein as a coagulant in patients with bleeding disorders. In another aspect the invention is directed to a method of treatment. . . of this invention is directed to an anticoagulant to neutralize the coagulant effects of endogenously released tissue thromboplastin by inactivating tissue factor protein .

DRAWING DESC:

DRWD(4)

FIG. 3. Cuticle bleeding times (CBT) in animals receiving tissue factor protein Arrows denote dose of tissue factor protein in U/kg. Pre refers to CBT prior to any injection.

DETDESC:

DETD(2)

As used herein, " tissue factor protein " refers to a protein capable of correcting various bleeding disorders, particularly those associated with deficiencies in coagulation factors. Tissue factor protein is distinct from tissue factor or tissue thromboplastin in that it lacks the naturally occurring lipid portion of the molecule. Tissue factor protein also includes tissue factor protein associated with phospholipid which lipid is distinct from the naturally occurring lipid associated with tissue thromboplastin and which displays coagulation-inducing capability without the concomitant toxicity observed with the lipidated protein. Infusion of tissue factor protein , as defined herein, does not result in disseminated intravascular coagulation. The capacity of tissue factor protein to correct various bleeding disorders is readily determined using various in vivo bleeding models e.g. initiation of coagulation in hemophilic. . .

DETDESC:

DETD(3)

The term " tissue factor protein antagonists" as used herein refers to substances which may function in two ways. First, tissue factor protein antagonists will bind to tissue factor protein with sufficient affinity and specificity to neutralize tissue factor protein such that it cannot bind to factor VII or VII.sub.a nor effect the proteolysis of factors IX or X when in complex with factor VII or VII.sub.a. Alternatively, tissue factor protein antagonists will inactivate tissue factor protein or the tissue factor/factor VII.sub.a complex by cleavage, e.g. a specific protease. Antagonists are useful, either alone or together, in. . .

DETDESC:

DETD(4)

An example of an antagonist which will neutralize tissue factor protein is a neutralizing antibody to tissue factor protein . Tissue factor protein neutralizing antibodies are readily raised in animals such as rabbits or mice by immunization with tissue factor protein in Freund's adjuvant followed by boosters as required. Immunized mice are particularly useful for providing sources of B cells for the manufacture of hybridomas, which in turn are cultured to produce large quantities of inexpensive anti- tissue factor protein monoclonal antibodies. Such tissue factor protein monoclonal antibodies have been prepared by Carson, S. D. et al., Blood 66(1), 152-156 (1985).

DETDESC:

DETD(5)

Tissue . . . This invention encompasses the treatment of various acute and chronic bleeding disorders by bypassing those deficiencies

through the administration of tissue factor protein . More particularly this invention is applicable to those bleeding disorders arising in animals deficient in various coagulation factors.

DETDESC:

DETD(6)

Tissue . . . native lipid using, for example, extraction with organic solvents. Examples of such organic solvents include pyridine. heptane-butanol mixture or ethanol. Tissue factor protein has been purified by chemical means. Examples of such chemical means are: treatment with detergents, such as deoxycholate or Triton. . . the presence of sodium dodecyl sulphate; concanavalin A bound to a Sepharose column; and, affinity columns using antibodies to the tissue factor protein or selective adsorption to factor VII. Included within the scope of tissue factor protein is tissue factor protein from recombinant or synthetic sources. Also included are dimers of tissue factor protein and tissue factor protein variants having amino acid substitutions and/or deletions and/or additions. organic and inorganic salts and covalently modified derivatives of tissue factor protein . Tissue factor protein produced by recombinant means may include a naturally occurring pro-form as well as a prepro-form of tissue factor protein .

DETDESC:

DETD(7)

For use in this invention tissue factor protein or tissue factor protein antagonists may be formulated into an injectable preparation. Parenteral formulations are suitable for use in the invention, preferably for intravenous administration. These formulations contain therapeutically effective amounts of tissue factor protein , are either sterile liquid solutions, liquid suspensions or lyophilized versions and optionally contain stabilizers or excipients. Typically. lyophilized compositions are. . .

DETDESC:

DETD(8)

Alternatively, for use in this invention tissue factor protein can be formulated into a preparation for absorption through the gastrointestinal tract. Such a preparation is suitable for use in the invention for oral administration. Such oral preparations contain therapeutically effective amounts of tissue factor protein , a lipophilic vehicle and a gastrointestinal tract absorption enhancing agent. Suitable lipophilic vehicles include mineral oil, triglycerides, esterified glycols, polyglycols. . .

DETDESC:

DETD(9)

Tissue factor protein may be administered by injection intravascularly or by oral administration at a dosage sufficient to correct a bleeding disorder, for example, replacement therapy in the face of a factor VIII deficiency. Tissue factor protein may be administered at a dosage sufficient to correct an acute bleeding incident in the face of a coagulation factor deficiency. Therapeutic dosage of tissue factor protein is in the range of about from 10 U/kg to 300 U/kg. A preferred therapeutic dosage of tissue factor protein is in the range of about 50 U/kg to 250 U/kg. A most preferred therapeutic dosage of tissue factor protein is in the range of about 75 U/kg to 200 U/kg. In the absence of an

international standard of tissue factor activity we have established a tissue factor standard. A unit of tissue factor activity is that amount of tissue factor protein in 10 .mu.l of tissue thromboplastin (commercially available from Sigma, St. Louis. Mo.) as measured by the chromogenic assay. See description of chromogenic assay below. The dose will be dependent upon the relative activity of the particular species of tissue factor protein , e.g., human tissue factor protein as compared to bovine tissue factor protein . The relative activities can be determined using the chromogenic assay. If, for example, human tissue factor protein is less active by one-half in an in vivo hemophilic dog model than the bovine tissue factor protein , then the therapeutic dosage range using human tissue factor protein would be increased by a factor of two. The dose will also be dependent upon various therapeutic variables including the animal species to be treated, the route of administration, the properties of the tissue factor protein employed. e.g. its activity and biological half life, the concentration of tissue factor protein in the formulation, the patient's plasma volume, the clinical status of the patient e.g. the particular bleeding disorder, and such. . .

DETDESC:

DETD(10)

Tissue factor protein antagonist may be administered by injection intravascularly at a dosage sufficient to correct a bleeding disorder, e.g DIC. Antagonists may. . .

DETDESC:

DETD(11)

Tissue factor protein also is suitably formulated into a topical preparation for local therapy for minor bleeding occurring from an accessible site in. . . conjunction with a cold application and gentle pressure. Such a preparation for local therapy includes a therapeutically effective concentration of tissue factor protein in a dermatological vehicle. The amount of tissue factor protein to be administered and the tissue factor protein concentration in the topical formulation, will depend on the vehicle selected, the clinical condition, the species of tissue factor protein used and the stability of tissue factor protein in the formulation.

DETDESC:

DETD(12)

The tissue factor protein or antagonist of this invention preferably is formulated and administered as a sterile solution although it is within the scope of this invention to utilize lyophilized tissue factor preparations. Sterile solutions are prepared by sterile filtration of tissue factor protein or by other methods known per se in the art. The solutions are then lyophilized or filled into pharmaceutical dosage. . . pH of the solution should be in the range of pH 3.0 to 9.5, preferably pH 5.0 to 7.5. The tissue factor protein should be in a solution having a suitable pharmaceutically acceptable buffer such as phosphate, tris (hydroxymethyl) aminomethane-HCl or citrate and the like. Buffer concentrations should be in the range of 1 to 100 mM. The solution of tissue factor protein may also contain a salt, such as sodium chloride or potassium chloride in concentration of 50 to 750 mM. The. . .

DETDESC:

DETD(13)

Tissue factor protein or antagonist preferably is placed into a container having a sterile access port, for example, an intravenous solution bag or. . .

DETDESC:

DETD(14)

Systemic administration of tissue factor protein may be made daily or several times a week in the case of replacement therapy for a coagulation factor deficiency. Administration is typically by intravenous injection Administration may also be intranasal or by other nonparenteral routes. Tissue factor protein may also be administered via microspheres, liposomes or other microparticulate delivery systems placed in certain tissues including blood.

DETDESC:

DETD(23)

The . . . milliliter fractions were collected at a flow rate of 2 ml/min. Fractions were relipidated and assayed for tissue factor activity. Tissue factor protein was eluted in approximately four (4) column volumes of eluant. The eluate was concentrated in an Amicon concentration cell using. . .

DETDESC:

DETD(26)

Purification of Tissue Factor Protein

DETDESC:

DETD(27)

Tissue factor protein was partially purified from bovine brain by a combination of acetone delipidation, Triton X-100 extraction, lectin affinity chromatography, and gel permeation chromatography. The highly purified tissue factor protein was 12,000 fold purified from brain powders (Table 1). A sensitive chromogenic assay for tissue factor protein was utilized to monitor purification steps. Following detergent extraction of acetone brain powders, the tissue factor protein activity could not be detected in the assay unless tissue factor protein was relipidated. The material which was infused into the rabbits had no cofactor activity prior to relipidation in either the. . . supra. Human placental tissue factor was isolated using known methods, for example, see Guha, A. et al. supra. Human placental tissue factor protein was compared to bovine tissue factor protein . As shown in Table 5. both human placental tissue factor and bovine tissue factor have a lipid requirement for activity. . .

DETDESC:

DETD(28)

Assay for Tissue Factor Protein

DETDESC:

DETD(30)

... bovine serum albumin (BSA) at a concentration of 1 mg/mL. This solution (PC/DOC) was used to relipidate tissue factor as follows. Tissue factor protein was diluted into TBS containing 0.1% bovine serum albumin (TBSA).

DETDESC:

DETD(32)

For the chromogenic assay, relipidated tissue factor protein samples were diluted in TBSA. Ten microliters were placed in a test tube with 50 .mu.l of the factor IX.sub.a. . .

DETDESC:

DETD(36)

Efficacy and Lack of Toxicity of Tissue Factor Protein in a Rabbit Model

DETDESC:

DETD(37)

Arterial . . . Triton X-100 was then infused into the first rabbit as a control while the second rabbit received 300 .mu.l of tissue factor protein . On relipidation, this would represent a dose of 233 tissue factor units per kilogram (U/kg). Sixty minutes after the infusion. . .

DETDESC:

DETD(38)

Rabbit . . . VIII antibodies in in vitro assay systems. These antibodies were then used to anticoagulate rabbits thus allowing the demonstration of tissue factor protein 's factor VIII by-passing activity in vivo. Thirty minutes after the infusion of anti-factor VIII antibodies, no factor VIII was detected. . . the arterial vein cannula. This resulted in profuse bleeding which took eleven min, to cease (Table 3). The animal receiving tissue factor protein (test #2, at Table 3) bled only slightly after the same treatment and this flow stopped after 38 seconds demonstrating that tissue factor protein by-passes factor VIII activity in vivo. The animals receiving tissue factor protein had no observed thrombi as had been reported in the literature and discussed above.

DETDESC:

DETD(39)

The toxicity of the tissue factor protein preparation was tested in six rabbits that were infused with 250 units of tissue factor protein per kilogram. After three days, no adverse effects were observed (Table 4). It should be noted that this is the. . . total of 120 hours of observation, demonstrating that the material is well tolerated and not toxic. Similar preparations of human tissue factor protein would therefore be expected to be well tolerated when infused into patients (Table 4) and be able to correct bleeding. . .

DETDESC:

DETD(41)

Efficacy and Lack of Toxicity of Tissue Factor Protein in a

DETDESC:

DETD(42)

Tissue factor protein is infused into hemophilic dogs using the procedure of Giles, A. R. et al., Blood 60, 727-730 (1982).

DETDESC:

DETD(43)

Lack of tissue factor protein toxicity was first determined in a normal dog on bolus injection of 50 tissue factor protein U/kg and 250 tissue factor protein U/kg doses. A cuticle bleeding time (CBT) was performed (Giles suora) prior to infusion and 30 min after each injection.. . . at various time points during the experiment (FIG. 3). In order to demonstrate in vivo factor VIII bypassing activity of tissue factor protein , experiments were conducted using hemophilic dogs. Fasting animals were anesthetized and a CBT performed prior to any infusion. Tissue factor protein was then administered by bolus injection and CBTs performed at various time points up to 90 min after the infusion. Several doses of tissue factor protein were administered. Blood samples were withdrawn throughout the duration of each experiment and assayed for factor V, prothrombin and partial. . .

DETDESC:

DETD(44)

An anesthetized normal dog was administered doses of tissue factor protein representing 50 and 250 U/kg of tissue factor protein on relipidation in the chromogenic assay. The CBT in this animal was approximately 3 min prior to any infusion (FIG.. . . unchanged at the end of the experiment and the CBTs were also within the normal range. Thus the infusion of tissue factor protein was well tolerated in normal dogs and no evidence of disseminated intravascular coagulation was found.

DETDESC:

DETD(45)

A hemophilic dog with a prolonged CBT characteristic of hemophilia A was administered 50 U/kg of tissue factor protein . The CBT was normalized 30 min after this infusion (FIG. 3). This correction was not associated with an alteration in. . . the CBT effect was again abnormal at this time point. A dose response relationship was established by infusion of 250 tissue factor protein U/kg. At this dose, the CBT of the hemophilic dog was normalized at 30 and 90 min (FIG. 3). This. . . a slight lengthening of the prothrombin time (Table 6). As a consequence, experiments were repeated using a dose of 100 tissue factor protein U/kg in order to obtain the maximum duration of efficacy while ensuring that other coagulation factor levels were unaffected. Thus, a hemophilic dog received 100 tissue factor protein U/kg and CBT performed at 15, 30 and 45 min. Interestingly, the CBT at 15 min was still abnormal (FIG.. . . Factor V levels, prothrombin times, thrombin clotting times and platelet levels were unchanged by the treatment. Thus, the efficacy of tissue factor protein in vivo was demonstrated at a dose which did not cause disseminated intravascular coagulation. The bypassing activity was confirmed in a third hemophilic dog using a dose of 100 tissue factor protein U/kg and CBTs performed at 30 and 45 min. While efficacy was established at both time points, some rebleeding occurred.

. .

DETDESC:

DETD(48)

Functional homology between bovine and human tissue factor proteins was shown using the chromogenic tissue factor assay. Bovine tissue factor protein was purified as described above Human tissue factor protein was partially purified from placentae using the method of Freyssinet et al, Thrombosis and Haemostasis 55(1):112-118 (1986) including affinity chromatography. . .

DETDESC:

DETD(50)

Protein concentrations in these samples were bovine tissue factor protein 0.59 mg/ml and human tissue factor protein 13.55 mg/ml. The difference in protein concentration was a result of differences in the degree of purification. These results are. . .

DETDESC:

DETD(52)

TABLE 2

Characterization of Partially Purified Tissue Factor Protein	Chromogenic Assay U/ml	Clotting Time Secs.
TBS/0.1% Triton buffer	0	250
Tissue Factor Protein	0	249
Relipidated TF	1,400	66.2

DETDESC:

DETD(53)

TABLE 3

Results of in vitro Tissue Factor Protein Bleeding Correction	Factor VIII U/ml	
No. Rabbit	Bleeding	
Infusion	Pre	
	30 min.	
	60. . .	

DETDESC:

DETD(54)

TABLE 4

Survival after infusion of Tissue Factor Protein	Time 0	72 Hours	120 Hours

				Infusion of TFP*		Survival
(+/-)	(kg). . .	0	+			
6	1.23	350	285	0	0	+

*Units were determined by chromogenic assay after relipidation of tissue factor protein samples.

DETDESC:

DETD(56)

TABLE 6

Blood Parameters in Normal and Hemophilic Dogs Following Bolus Injection of Tissue Factor Protein

	Dose Tissue Factor Protein	Sample Time Post Infusion	PT	PTT	Factor V	Platelets
Dog	(U/kg). . .	15	13	51	1.23	169
		57	13	51	1.17	223

Coagulation assay results after bolus injection of tissue factor protein in normal and hemophilic dogs.
N = normal dog
H1 and H2 = hemophilic dogs
ND. . .

CLAIMS:

CLMS(1)

We . . .

congenital coagulation disorders, acquired coagulation disorders, and trauma induced hemorrhagic conditions, comprising administering a therapeutically effective dose of a sterile tissue factor protein composition isotonic to blood, substantially devoid of the naturally occurring lipid of tissue factor and possessing substantially no procoagulant activity. . .

CLAIMS:

CLMS(3)

3. The method of claim 1 wherein the tissue factor protein is administered intravenously or orally.

CLAIMS:

CLMS(7)

7. . . . consisting of congenital coagulation disorders, acquired coagulation disorders, and trauma induced hemorrhagic conditions, comprising a therapeutically effective does of human tissue factor protein , substantially devoid of the naturally occurring lipid of tissue factor and possessing substantially no procoagulant activity prior to administration, and a pharmaceutically acceptable vehicle characterized by conferring substantially no procoagulant activity on the tissue factor protein prior to administration.

CLAIMS:

CLMS(11)

11. . . . administration to an animal with a bleeding characterized by a tendency to hemorrhage comprising a therapeutically effective dose of human tissue factor protein substantially devoid of the naturally occurring lipid of tissue factor and possessing substantially no procoagulant activity prior to administration, and a pharmaceutically acceptable vehicle characterized by conferring substantially no procoagulant activity on the tissue factor protein prior to administration in combination with a container having a sterile access port.

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è@mr)(g2lwy)(g2lwy)(t2hwr)(t2hwr)(t2hwr)(t2hwr)(a2swn)(a2swn)(t2hwr)t(h2rw)(v2awl
L6 (60186)MET
L7 (3758)GLU
L8 (3990)THR
L9 (11638)PRO
L10 (4864)ALA
L11 (3253)TRP
L12 (0)MET(2W)GLU(2W)THR(2W)PRO(2W)ALA(2W)TRP
L13 (489762)SER
L14 (4805)GLY
L15 (3990)THR
L16 (3990)THR
L17 (2723)ASN
L18 (3990)THR
L19 (4586)VAL
L20 (0)SER(2W)GLY(2W)THR(2W)THR(2W)ASN(2W)THR(2W)VAL
L21 0 MET(2W)GLU(2W)THR(2W)PRO(2W)ALA(2W)TRP OR SER(2W)GLY(2W)THR
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